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Circadian Rhythm Desynchronosis, Jet Lag, Shift Lag, and Coping Strategies (Reprint)

By

Carlos A. Comperatore

and

Gerald P. Krueger

Biomedical Applications Research Division

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United States Army Aeromedical Research Laboratory
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Reviewed:

Dennis F. Shanahan

DENNIS F. SHANAHAN
LTC, MC, MFS
Acting Director, Biomedical
Applications Research Division

Dennis F. Shanahan

DENNIS F. SHANAHAN
LTC, MC, MFS
Chairman, Scientific
Review Committee

Released for publication:

David H. Karney

DAVID H. KARNEY
Colonel, MC, SFS
Commanding

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Jet lag and shift lag have similar physiological consequences, but shift lag is a more complex problem. The most severe desynchronization may be experienced by airline personnel making transmeridian flights. Coping strategies for eastward and westward travelers and for shiftworkers are recommended, as are interventions involving melatonin.

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CARLOS A. COMPERATORE, PHD
GERALD P. KRUEGER, PHD

CIRCADIAN RHYTHM DESYNCHRONOSIS, JET LAG, SHIFT LAG, AND COPING STRATEGIES

From the U.S. Army Aeromedical Research Laboratory
Fort Rucker, Alabama

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Reprint requests to:
Carlos A. Comperatore, PhD
U.S. Army Aeromedical Research Laboratory
Fort Rucker, AL 36362-5292

BACKGROUND

The human body uses predictable environmental events such as sunrise and sunset to maintain a consistent internal organization of physiological functions. Peak levels of physiological rhythms are specifically timed to occur at the appropriate phase of the daily light/dark (LD) cycle. This internal synchronization of physiological rhythmicity results in the availability of metabolic energy, neurotransmitter synthesis, enzyme activity, and hormone production at critical times of the day. The mechanism that mediates the interdependence of human physiology with environmental cycles of light and dark has been referred to as the circadian timing system (CTS).[55] It is generally accepted that the CTS synchronizes physiological and behavioral rhythms to a circadian period (*circa*, about; *dies*, a day) and that the phase of these rhythms can be reset by the influence of the environmental LD cycle. Other environmental rhythmic cues (e.g., social interaction, meal timing) also serve to synchronize the CTS, but the LD cycle is of overriding importance.

The Human Circadian Timing System (CTS). The CTS is composed of structures such as the suprachiasmatic nuclei (SCN) and the pineal gland, which together contribute to the synchronization of physiological and behavioral rhythms. These structures are usually referred to as oscillators or biological clocks because of their periodic contribution to the generation of circadian rhythmicity. Research on the mechanism of CTS function suggests that this system is composed of coupled multiple oscillators, many of them yet unknown. Cyclic environmental events with periods of approximately 24 hours, such as the earth's LD cycle, entrain (or synchronize) the rhythmic output of the CTS. In the absence of the entraining influence of sunrise and sunset or social cues, the CTS endogenously maintains physiological and behavioral rhythmicity (e.g., sleep/wake cycle and rhythms of REM sleep, body core temperature, plasma cortisol, adrenalin, noradrenalin, and melatonin) with a period of approximately 24 hours.

In humans, under normal LD cycles, physiological and behavioral rhythms exhibit consistent peaks (acrophases) and troughs in either the day or the night (light or dark phase of the LD cycle). Table 1 is an extensive, but not exhaustive, list of physiological and behavioral rhythms. Several of these rhythms (e.g., activity/rest, body core temperature, adrenalin and noradrenalin production, vigilance, decision making, problem solving) exhibit peaks in the light phase of the LD cycle (diurnal). Others, such as the hormone melatonin, exhibit peak levels during the night phase (nocturnal) of the LD cycle.[55,86]

Internal and External Synchronization. Under a consistent environmental LD cycle, physiological and behavioral rhythms maintain a relative synchronization with each other (internal synchronization) and with the daily rhythm of sunrise and sunset (external synchronization). That is, in steady state conditions, they exhibit their peaks and troughs at approximately the same time of day or night, depending on their natural expression. If meal times are regular and sleep periods are consistent, other physiological rhythms such as premeal duodenal disaccharidase activity and motility also contribute to the establishment of internal synchronization.[19,70] In steady state, it is possible to maximize the ability to maintain normal energy levels and the best possible state of health.

DESYNCHRONOSIS: JET LAG AND SHIFT LAG

Workers often forfeit the comfort of internal and external rhythm synchronization in situations that require an alteration of the activity/rest cycle (day: activity; night: rest). Two categories of work-related circadian rhythm disruption are common: (1) transcontinental or international travel necessitating rapid changes in the phase of the light/dark cycle (e.g., transmeridian flights) and (2) transition in a shiftwork rotation schedule that changes the activity/rest cycle (e.g., altering workshifts from days to evenings or nights).

Individuals who engage in rapid transmeridian travel (e.g., international business-people, airline crews, and military personnel) undergo alterations in the timing of the CTS. These changes manifest in the desynchronization of physiological and behavioral rhythms. Upon arrival, travelers encounter a new rhythm of sunrise and sunset and a time-altered activity and social schedule. The impact of these changes on body physiology results in several days of fatigue, sleepiness, lethargy, insomnia, gastrointestinal track disorders, and poorer mental agility and performance. The syndrome is commonly known as **jet lag**.[88] Essentially, the body takes a while to synchronize its rhythms to the new time zone.

Similarly, shiftworkers (e.g., factory workers, police officers, hospital attendees, communication technicians) who alter their work schedule to include duty during the evening or night, also disrupt the synchronization of the CTS, with results resembling jet lag. Shiftwork changes usually disrupt the timing of sleep and activity and have noticeable effects on alertness, fatigue, and work

TABLE 1. Physiological and Behavioral Rhythms Exhibiting 24-Hour Periodicities

Rhythm	Acrophase
Sleep/Activity	
Sleep	Night
REM sleep	Night
Exercise capacity	Day
Activity	Day
Endocrine Metabolism/Homeostasis	
Core temperature	Day
Urine production	Day
Catecholamine excretion	Day
17-Hydroxicorticosteroid excretion in plasma and urine	Day
Electrolyte and corticosteroid excretion in urine	Day
Melatonin synthesis	Night
Adrenalin and noradrenalin production	Day
Cognitive performance	
Addition of numbers	Day
Auditory vigilance	Day
Decision making	Day
Reasoning	Day

effectiveness. Kogi[47] refers to the detrimental effects of shiftwork changes as "shift lag" because of the similarity with the jet lag syndrome both in generation and symptomology.[47,89]

The adverse effects of jet lag and shift lag result from the desynchronization of physiological and behavioral rhythms, a condition referred to as internal dissociation or, by some authors, circadian rhythm **desynchronosis.** Although jet lag and shift lag are both forms of desynchronosis, they are somewhat different from one another. The transmeridian traveler experiences a rapid change in the timing of sunrise and sunset (LD cycle) and has to adjust, often only briefly, to the destination's schedule of life events. On the other hand, the shiftworker has to adjust to (1) a change in work schedule (e.g., day to evening or night, night to day or evening), (2) a change in sleeping schedule (often from nighttime to daytime), and (3) family and societal schedules that are mostly diurnal. Shiftworkers exacerbate the body's adjustment by changing schedules again on off-duty days (e.g., weekends) in an attempt to maintain a normal social life.

Desynchronosis adversely affects worker performance and health. Today, with the volume of work-related international travel, jet lag directly impacts on the effectiveness of many business interactions. At the least, jet lag has become a commonplace nuisance in international business. At worst, for international airline pilots and crews who travel back and forth across time zones, jet lag, when combined with shift lag, may affect the safety of airline travel.[30,31] (Pilot scheduling and airline safety are discussed in depth in Chapter 10).

Shift lag, too, is an increasing problem in occupational medicine. Research on the performance implications of human circadian rhythms, and on the medical and social difficulties experienced by shiftworkers, clearly suggests that it is important for occupational medicine specialists to understand shift lag and possible preventive measures.[79-81]

The long-term health risks associated with continued use of shiftwork schedules are becoming better known.[45,47,48,52,67-69,89] The physiological impact of rotating shifts particularly affects nightworkers, whose rhythms of body temperature and sleep do not completely reverse to match their duty schedules.[43,44,84]

Among nightshift workers, the immunological functions of lymphocytes in peripheral blood show a circadian variation and are lowered at night.[56] Gastrointestinal diseases such as gastric or duodenal ulcers occur more frequently among these workers.[1,6] Shiftworkers, in general, complain more frequently of respiratory and motor organ disorders, shortages of quality sleep, increased fatigue levels, and lapses in performance (for review see Chapter 6 and Kogi[47]).

International travelers, employers of shiftworkers, and many employees themselves may underestimate the impact of desynchronosis associated with jet lag and shift lag. This chapter reviews the mechanism of generation of both jet lag and shift lag and highlights the complexity of coping with desynchronosis.

Transmeridian Flights and Desynchronosis (Jet Lag). Because the earth rotates on its axis every 24 hours, the globe has been divided into 24 one-hour time zones, each with 15 meridians. Daylight travels from one meridian to another in 4 minutes. Therefore, individuals who travel rapidly across several time zones can expect not only a change in their activity/rest rhythm to accommodate to the new time zone, but a change in the environmental LD cycle as well. On the day of travel eastward travelers experience a reduction of day length while their bodies respond as if they were still in the departure time zone (they lag behind).

To adjust the body's rhythms to an eastward destination the CTS needs to be ***advanced*** as many hours as time zones crossed. In contrast, westbound travelers experience an extension of the day of travel. In this case, adjustment of the CTS to the destination time zone requires a ***delay*** of as many hours as time zones traversed.[88]

The greater the number of time zones traversed in a single day, the greater the time adjustment required for the resynchronization of internal rhythms with the new LD cycle and activity/rest cycle. The human CTS can adapt to advance or delay shifts of no more than 60 to 90 minutes per day.[10,11] Beyond this range, the CTS begins to lag behind the LD cycle and internal desynchronization ensues.[40,42] The inability of the human CTS to rapidly readjust beyond its limits of entrainment results in a transitional period of desynchronosis, commonly referred to as jet lag. This syndrome usually lasts a few days, but depending on the number of time zones crossed and individual differences, it may last up to 18 days.[12,39]

Since activity/rest rhythms exhibit an endogenous period greater than 24 hours (approximately 25 hours per day), it is easier to adjust to westbound travel, which results in a longer travel day. Eastward travelers experience a shortening day and longer resynchronization periods.[41] The severity of jet-lag desynchronosis symptoms depends on the amount of time shift and on individual chronotypic characteristics (see Table 2). For example, after flying eastward across six time zones from New York to Europe, on the day of arrival at 0900 the body's CTS still functions as it would at 0300 in New York (it lags behind), and the traveler undoubtedly is very sleepy. Conversely, if local time is 2400 and the body's biological time is 1800, the traveler will likely have trouble falling asleep.

Travelers who fly over the top of the Arctic Circle cross more time zones faster and sometimes experience even more dramatic symptoms, including disorientation, decreased concentration, and muscle aches.[15] For example, crossing 11 time zones on a 10-hour flight from Europe to Alaska would produce the full range of jet-lag symptoms and require at least one week to adjust; yet passengers flying from North to South America, staying within one or two time zones, may experience fewer and less acute jet-lag symptoms.

TABLE 2. Factors Influencing Rate of Adjustment to Time Zone or Shift Change

Direction of change (time advance or delay)[40,86,87]
Rhythm stability (stable or labile)[78]
Rhythm amplitude (low or high)[5,86,87]
Personality traits (extraversion or introversion, neuroticism)[16,34]
Rhythm chronotype (morning person or evening person)[16]
Age (young or old)[33]
Motivation (high or low)[30]
Sleep habits (rigid or flexible)[27,28]
Performance task (high or low cognitive load)[27,30]

Effects of Jet Lag on Performance. Rapidly crossing time zones affects both physiological and performance rhythms. The latter are of major operational significance when people are required to carry out complex psychomotor or intellectual tasks soon after arrival. In general, psychomotor performance after a 6-hour transmeridian flight suffers a reduction of 8–10% of preflight levels during the first day after arrival. This is disquieting because such impairment is comparable to that observed when the blood alcohol concentration is 0.05%.[41] In general, several performance rhythms (see Table 3) have been shown to be adversely affected after both westward and eastward transmeridian flights, but

TABLE 3. Performance Degradation Effects of Time and Schedule Changes

Subjects and Alterations	Degradation Effects
Pilots and students 6 time zones eastward	Flight simulator skills 24 h, means 3–4% from preflight Reaction time Complex sensory motor skills (to operate simulator) Digit summation Digit cancelation
6 time zones westward	Psychomotor performance in simulator reduced Digit summation Digit cancelation
6–9 time zones eastward	Efficiency in simulator performance reduced Psychomotor performance 1.8–3.5% from preflight Hand-eye coordination, 8% from preflight
Military personnel 6 time zones eastward	50% of personnel experienced fatigue and sleep difficulties; 40% reported subjective weakness Dynamic arm strength reduced by 6.1–10.8% Elbow flexor strength reduced 8.4–12% Lift and carry tasks reduced 9.5% Logical reasoning reduced 15%
Student volunteers 2–4 h phase change of sleep/wake period	Significant decrement in vigilance, calculation proficiency, mood
Female volunteers 8 h advance of sleep/wake period	Short-term memory reduced Visual search performance reduced
Student pilots 2.5 h advance of sleep/wake period	Sleep impairment 35% increased errors in flight performance 1–15% decrease in letter cancelation
Nurses Reversal of sleep/wake period; shift from day to night duty	Short-term memory reduced

eastward travel has more pronounced effects. Upon arrival, westward time-zone crossings usually affect performance during the afternoon and early evening hours, whereas eastward crossings affect performance during the morning and early afternoon hours.[41] In general, these effects have been shown to persist up to 5 days postflight, but differences between pre- and postflight performance are not significant 3 days after arrival.

Partial adjustment of these rhythms can be observed on the first day after arrival. However, after eastward flights inducing a 6-hour phase advance, readjustment is slower than after a 6-hour westward flight (phase delay).

COPING WITH JET LAG

Monk[54] distinguishes several jet-lag stress effects stemming from the particular physical and psychological aspects of international travel (e.g., making connections at airports, luggage hassles, and customs checks) and the flight itself (e.g., dehydration, changes in altitude effects) from those that are a product of the need to reset the biological clock upon arrival (i.e., CTS desynchronosis). Since circadian rhythm desynchronosis involves the loss of internal and external synchronization, coping strategies must ameliorate both physiological and cognitive effects associated with the jet-lag syndrome. The following strategies help alleviate jet lag.

Adjusting to the New Time Zone. Transmeridian travelers who expect to remain in the new time zone for weeks should quickly change the timing of behavior patterns to match local events; that is, sleep and wake-up times, meal times, and social events should match local schedules as soon as possible. To speed up the rate of readjustment, it is necessary to (1) immerse oneself in local society, maintaining normal social activity patterns, (2) engage in physical exercise, and (3) maintain regular exposure to daylight.[38,86] Outdoor activities are recommended because daylight assists in the adjustment of melatonin rhythms (see "Pharmacological Alternatives," below), which significantly contributes to the resynchronization of the CTS.[49,73] Late wake-up and sleep times and social isolation impede adjustment and are therefore discouraged.[40] Lastly, following local meal schedules significantly aids in the process of resynchronization.[29]

Because it takes several days to adjust to jet lag, it is recommended that travelers arrive a few days early to allow time for the CTS to resynchronize before they conduct important meetings, negotiations, or other business that may require decision making.

Remaining on Home Base Time. In certain circumstances, travelers can attempt to maintain the time schedule of their departure location by not resetting their watches and by scheduling events, meals, and sleep times to match their home base clocks. This technique avoids most of the CTS disruption of travel except for the change in LD cycle. For compatibility with societal expectations, it is often difficult to arrange things in the new environment to the traveler's own time preference. However, a California businessman can arrange late afternoon meetings on the East Coast on the day of travel, and a New York worker can conduct business at midday on the West Coast.

Sleep Timing. Because getting uninterrupted restful sleep upon arrival is often difficult, the traveler should be fully rested at departure so that there is no "sleep debt."[54] A wristwatch can be set to the destination time zone and activities pursued according to the new clock time. Bedtime should be shifted progressively earlier each night (phase advance) for a few days before an eastward flight and progressively later (phase delay) in anticipation of a westward flight. The time of awakening must also be adjusted.

On long flights, naps should be short to avoid interfering with sleep planned for the first night after arrival. Upon arriving, it is recommended to remain awake until normal bedtime for the destination time zone.

Meal Timing and the Use of Diets. Diet has been proposed to be useful in the amelioration of jet-lag symptoms,[23] particularly because certain foods (carbohydrates) induce sleep by facilitating serotonin synthesis and others (proteins) promote alertness by stimulating the synthesis of catecholamines. Within this context, choice of diet before and during the trip may help in the adjustment to the destination's timing of life events such as sleep and meal schedules.

Diet has not, however, been shown to aid in actual resynchronization of the CTS. Recent research in circadian rhythms of the gastrointestinal (GI) track of rats indicates the existence of a motility rhythm that can be entrained by the consistent timing of meals.[19] Irregular contractions (IC), possibly similar to hunger contractions in humans, recorded from the antrum and duodenum, were shown to occur throughout 3, and sometimes 5, hours before a scheduled meal. The involvement of a biological clock in the timing of these contractions was shown during phase shifts of meal timing and fasting. Transient changes in the phase of the IC rhythm lasting 4 to 6 days were observed after delays in meal timing of 6 and 8 hours; such delays were similar, for humans, to eating dinner later after a westward flight. In addition, the IC rhythm exhibited a circadian variation during food deprivation. Similar experiments with rhythms of duodenal dissacharidases also indicate the influence of a biological clock on physiological rhythms of the GI track.[17] Consequently, resynchronization of the GI track after changes in meal timing must be treated in a similar form as resynchronization of rhythms driven by the suprachiasmatic nuclei (SCN). In both cases the timing of the exogenous environmental cycles, light/dark for the SCN and feeding/fasting for the GI track, is critical for the reestablishment of steady state synchronization. Although choice of meals may possibly aid in inducing sleep or alertness, it is the consistent timing of meals and fasting periods that will serve as phase information for the oscillator influencing the GI track and that will ultimately play a significant role in facilitating CTS resynchronization.

Bright Light Therapy and Jet Lag. In 1980, Lewy and co-workers[49] demonstrated that high irradiances (1000 lux) of broad-spectrum white light influence human endocrine function, specifically secretion of the hormone melatonin (see "Pharmacological Alternatives," below). This finding implied that bright artificial light influenced the SCN and its control of pineal activity. The SCN receives light/dark cycle phase information by way of the retinohypothalamic tract and regulates pineal function via a multisynaptic pathway and the paraventricular nucleus of the hypothalamus, the superior cervical ganglia, and sympathetic fibers ending in the nervi coronarii innervating the gland. Consequently, because the SCN has been associated with synchronization of endogenous physiological rhythms to the exogenous influence of sunrise and sunset, bright artificial lights may be used to mimic the destination LD cycle before the transmeridian flight. In this manner, travelers may reduce the desynchronosis experienced upon arrival. Conceivably, aircraft passenger cabins specially configured with bright lights could speed up CTS entrainment on overseas flights; such cabins may have special military applications.

SHIFTWORK SCHEDULES, LIGHT/DARK CYCLES, AND DESYNCHRONOSIS

Shiftwork and Shift Lag. Historically (circa 1890s), two alternating teams of employees, each working 12 hours per day, (0600–1800 and 1800–0600) 7 days per week, kept industries such as steel mills operating continuously.[4] After World War I, operations were divided into three 8-hour shifts per day, with employees working 7 days or 56 hours per week. Since World War II, shifts work a conventional 40-hour work week combining any five 8-hour workdays of the 7-day week. Three different teams work 8 hours per shift with a 1-hour or shorter rest and meal break midshift: 0730–1630 (dayshift), 1530–2430 hours (evenings) and 2300–0800 (nights). To provide continuous operations (CONOPS), many different schemes are used to rotate employees from one shift to another[83] and to determine which 5 of the 7 days in the week they work. The schemes ensure that workers work each schedule equally.

Traditional shiftwork schedules fail to account for many circadian rhythm variables, especially the limitations of sleep/wake cycles. In particular, shifting between day- and nightwork results in sleep disruption, decreases alertness on the job, and interferes with established family and social activity schedules.[83]

In a common shiftwork weekly schedule change, each employee works 7 consecutive nights, followed by 2 days off; then 7 evening shifts, followed by a day off; then 7 consecutive day shifts, followed by 4 days off (7N–2 Off–7E–1 Off–7D–4 Off).[15] If a worker begins this schedule on a Wednesday, a 4-day weekend—Saturday, Sunday, Monday, Tuesday—serves as the only weekend respite in four weeks. The schedule includes a stretch in which employees work 14 or 15 days with an average work week of 42 hours. Workers rotate shifts every week, but they experience shift lag upon each weekly change. Coleman and Czeisler call this the "weekly phase advance" schedule because it forces employees to advance their work schedule eight hours earlier in the ***counterclockwise*** (backward) direction (nights to evenings to days) each week.[15] In effect, at shift change, the body must adjust to a shorter day, necessitating going to bed earlier than normal.

Regularly changing shiftwork schedules (e.g., from day- to nightshift) bring about sudden substantial rescheduling of the activity/rest rhythm and meal times. Depending upon the circumstances, the most immediate consequence is redistribution and especially loss of sleep due to changes in sleep and wake-up times. In addition, synchronization of body core temperature with the activity/rest rhythm is disrupted because temperature rhythms adapt very slowly to new schedules,[17,18,84,89] whereas activity/rest rhythms are immediately altered by changing sleep and wake-up times.

After transmeridian travel, the synchronicity of the new LD cycle and social cues with the local sleep/wake cycle promotes readjustment of travelers' CTS to diurnal activity. In contrast to transmeridian travel, after a shiftwork change from day- to nightshift, the temporal relationship between sunrise and sunset and the new sleep/wake schedule is in conflict. Internal synchronization is lost, and external synchronization to the LD cycle is also severely disrupted. Cognitive performance usually deteriorates with changes in shiftwork schedules because its 24-hour distribution becomes desynchronized relative to the new activity/rest rhythm.[24-26] Thus, after changes in work schedules, the shift-lag syndrome persists until the CTS resynchronizes to the new duty/rest schedule. This process is made more difficult during shift lag than during jet lag because daily exposure to sunlight tends to entrain the SCN to diurnal activity.

Aviation Crews, Jet Lag, and Shift Lag. Commercial and military air crews must be able to perform safely and effectively at various times of the day and night that are often in conflict with their circadian rhythms. Pilots frequently fly "long-haul" routes through the night, across multiple time zones, and experience jet lag upon arrival. Graeber[31] points out that many pilots begin 3- to 4-day trips with a slight sleep debt, and they accumulate a substantial amount of sleep loss during a trip. On short layovers, rest time often is inadequate, and its timing in conflict with the preflight sleep/wake cycle. That is, it is difficult to sleep when the body temperature is rising. Lodging accommodations are not always conducive to restful sleep, and amounts and quality of sleep often are inadequate.

Soon, after short layovers, pilots resume flying, sometimes in the same direction, but more often on a return trip in the reverse direction across the same time zones just traversed. Resulting circadian rhythm desynchronization can have a variety of effects on individual crew members, including disturbances in manual flying skills.[31] Klein et al.[37] showed clear directional differences in disruption of performance in postflight simulator tests and in the rate of recovery in the new time zone. Flight simulator performance was more degraded after an eastward return flight than after a westward outbound flight.

Some pilots and crew members not only work unusual flight schedules imposed by their employers but add to their CTS desynchronization by becoming long-haul commuters. Some of them fly as passengers from their residence across time zones to report to work at their employer's home base airfield. There, they "begin" their several days of scheduled flying. When these same pilots get rescheduled for flights departing at substantially different times of the day, they subject themselves to complicated interactions between jet lag and shift lag, become fatigued, and are likely to put themselves and their passengers at risk.

COPING WITH SHIFT LAG

Various countermeasures can prevent shift-lag desynchronosis or, when it is inevitable, can facilitate coping with or adjusting to it. We include practical and optimal coping strategies without limiting the scope to procedures that are most economical to the industrial community.

Fixed Shift Schedules. One countermeasure to prevent shift-lag desynchronosis is for employees *not to change shift times at all.* People may choose from many available jobs that do not involve rotating shiftwork schedules. A select few CONOPS industries lock into a fixed shift system whereby some employees work exclusively nights or evenings for extended periods, months, even years at a time.

With a steady work schedule the presumption is that desynchronosis should not be a problem. Research indicates, however, that the circadian distribution of physiological rhythms does not completely reverse even after several months on nightshift. The body's core temperature rhythm does not exhibit a complete reversal with a nocturnal redistribution of its acrophase. In most cases, acrophase tends to occur at the beginning of the nocturnal work period but drops abruptly thereafter.[84] Even in cases of consistent long-term schedules, body temperature is not fully inverted; instead, a nocturnal tendency of the acrophase is followed by a flattening of the rhythm.[2,43,66,84] It is not clear how much of the temperature pattern is self-induced by nightworkers, who, on their off-duty days, revert to a day schedule, altering their meal and sleep times to accommodate other societal expectations.[82]

Decreased Rate of Rotation. Most CONOPS organizations rotate employee shifts weekly. Changing schedules every 3 to 4 weeks would allow more time for CTS adjustment between less frequent shift changes. Workers who are able to maintain similar sleep and wake-up times during off-duty days are more likely to exhibit consistent physiological adaptation than those who change meal and sleep times to a diurnal schedule on their off-duty days. Staying on schedule allows rhythms of body temperature and of rest and activity to maintain a constant relative syncrhonization after initial adaptation. Performance is then more consistent from one workday to another.

Clockwise or Forward Rotation of Shifts. For many years industrial plants used a "phase advance" (counterclockwise: days to nights to evenings), backward shift rotation system.[85] Circadian rhythm principles suggest that workers should instead rotate toward later shifts in a *clockwise,* forward (days to evenings to nights) "phase delay" fashion. That is, because the body naturally adjusts its free-running rhythms toward a longer day (25 hours), it is easier to delay the time one goes to bed for about 3–4 hours (for clockwise shift changes) than it is to move bedtimes counterclockwise to earlier hours. Thus working days, then evenings, and then nights permits an easier circadian rhythm adjustment to a new schedule.

Slow Drift Rotation. To avoid weekly abrupt 8-hour shift transitions, Coleman and Czeisler recommend that workers make a gradual transition to the new shift by starting work 2½ hours later than on the previous day the last three days before the actual change to a new schedule. Coleman,[15] however, suggests that this kind of schedule is hard to get used to; it makes it difficult for workers and their families to anticipate when the employee is to be working and when off duty.

Rapid Rotation. In quick succession, employees are expected to work 1 or 2 dayshifts, then 1 or 2 evenings, followed by 1 or 2 nights. This rapid clockwise rotation purports to allow circadian rhythms to remain synchronized with the dayshift.[15,83] Employees do not spend enough time on the evening or night schedules for their internal rhythms to adjust to nightwork. That is, the diurnal acrophase of the body temperature rhythm is not noticeably altered, internal synchronization is not lost, and disruption of sleep/wake cycles is only slight.[26] Workers tough out the nightshift and rotate quickly through it, but during the night they experience lowest daily body temperatures, increased fatigue, and a considerable decrement in performance.

For more detailed review of the problems of shift lag and coping strategies, see Chapter 12.

RESYNCHRONIZATION RATE FOR ADJUSTING TO JET LAG AND SHIFT LAG

The rate of adjustment to changing light/dark cycles or shift schedules depends on a number of physiological and individual factors (see Table 2).[88]

Phase Delay Versus Phase Advance. In general, the human CTS exhibits a preference for quicker reestablishment of internal syncrhonization after a ***delay*** in the activity/rest rhythm or the LD cycle. Consequently, the human CTS readjusts more rapidly when crossing time zones traveling west. Similarly, changing from morning to evening to night schedules (phase delay) is more desirable than the reversed pattern of change (phase advance).

Individual Differences. People who are more apt to rapidly adjust to changing LD cycles and rotating work schedules are distinguished by rhythm amplitude and stability and by their wake-up time preference. Some researchers suggest that low-amplitude body temperature rhythms may identify people with a tendency to adjust rapidly to changes in the activity/rest schedules.[9,65,86,88]

In contrast, some workers tolerate long-term shiftwork without experiencing sleep disturbances even after 25 years. Unlike people who can rapidly reentrain to changing work schedules, these workers exhibit large-amplitude body temperature rhythms and adjust slowly to new schedules. They suffer short-term desynchronosis but experience fewer sleep and work-performance alterations after resynchronization owing to the stability of their circadian rhythms.[5,63]

Russian researchers developed a method to measure rhythm stability.[77,78] People can be classified into three categories—"inert," "intermediate," and "labile"—depending on the stability of their rhythms. Inert people have more rigid circadian rhythms; they experience more difficulty during rapid changes of work schedules or crossing of time zones than their labile counterparts.[76–78] Intermediate individuals fall somewhere between the two extremes.

Morning people ("larks"), with strong preference for early morning wake-up times, exhibit early morning peaks and large amplitudes in their temperature rhythms. These characteristics make the circadian system rigid and result in greater resistance to resynchronization. In contrast, evening people ("owls") appear to have a more labile circadian system exhibiting smaller amplitudes in temperature rhythm than "larks"; their peaks occur later in the day.[35]

In general, young extroverted people exhibiting labile rhythms and an affinity for late morning awakening ("owls") and having flexible sleeping habits and high motivation are more apt to readjust rapidly to sudden changes in light/dark cycles or work schedules. On the other hand, the choice between rapidly changing and long-term shiftwork schedules becomes an operational question affected by the type of work (whether lowly or highly cognitive tasks), the duration of individual shifts, the total duration of shiftwork (whether it is chronic or temporary), and the individual characteristics (rhythm chronotypes) of shiftworkers employed.

PHARMACOLOGICAL ALTERNATIVES

The Problem of Rapid Resynchronization of the CTS. The central problem in ameliorating the desynchronization syndrome is rapid and complete reestablishment of internal synchronization. Both internal and external synchronization can be recovered by inducing significant changes in the timing of the CTS. This concept applies for rapid crossing of time zones during transmeridian flights and for dramatic changes in shiftwork schedules (going from day- to nightshifts).

The most immediate problem of the transmeridian traveler (eastward and westward) is to rapidly adjust the sleep period to coincide with the destination night and to obtain sufficient restful sleep on that new schedule. Nightshift workers must sleep during late morning and afternoon hours, and evening shiftworkers must sleep in the early and late morning hours. In these cases, the change in timing results in desynchronization of the temperature and activity/rest rhythms, as well as of the many rhythmic physiological functions controlled by the circadian timing system (Table 1). Consequently, any drug used against desynchronization must quicken the resynchronization rates of various rhythms that are dependent on the CTS, and in particular that of the body's temperature rhythm.

Hypnotics induce sleep but do not necessarily resynchronize the CTS. Complete resynchronization of the CTS not only induces sleep, but also reestablishes the normal architecture of the sleep period, total sleep time, sleep continuity, normal sleep inertia, and normal relationship of the acrophase of the body core temperature rhythm with the activity phase of the sleep/wake cycle. Consequently, a drug that artificially induces sleep does not alter the physiological and cognitive consequences of desynchronosis if it does not influence the timing of the CTS. Sleep induced by hypnotics masks the status of the CTS, which may remain desynchronized with the new schedule. The restorative value of such a sleep period may also be questioned because endogenous physiological rhythms are still in the process of resynchronization. In fact, the use of a synthetic substance that may influence the activity and effect of endogenous neurotransmitters (e.g., benzodiazepines affect GABA receptors) may retard the process of resynchronization (not often studied in human volunteers). In brief, the evaluation of potentially chronobiotic drugs (those that affect the CTS) depends upon their effects on the process of CTS resynchronization, and not simply on their effects on individual symptoms associated with desynchronosis (e.g., sleep loss and fatigue).

One variable that reflects CTS phase status with relation to a new work schedule or LD cycle is body core temperature. Consequently, following changes in the phase relationship of the temperature rhythm with a newly implemented schedule after the administration of a drug is likely to reflect the influence of the drug on the status of the CTS. Proper phase relationships between the temperature rhythm and the activity/rest rhythm imply that normal sleep patterns may have been reestablished. The effects on cognitive performance must also be considered since cognitive degradation is one of the most detrimental consequences of desynchronosis in terms of individual and industrial productivity. Unfortunately, very few studies with human subjects provide this information.

Current Pharmacological Alternatives. Although, there is not enough clinical evidence that any chronobiotic drug rapidly resets the CTS, or all of the rhythms under its control, a number of substances appear to be potentially helpful in combatting desynchronosis.[64]

Benzodiazepines are currently used to combat desynchronization. Temazepam has been effective to induce sleep in humans without severe side effects.[51] Two desirable characteristics of temazepam are its short half-life (5–8 hours) and the fact that its metabolism does not result in active metabolites.[13] Psychomotor performance after single doses of temazepam (5, 15, and 30 mg) was somewhat impaired after the 30-mg dose up to 2 hours postadministration.[50] In a visuomotor task, Nicholson and Stone[58] showed that single administrations (10, 20, and 30 mg) of temazepam had no significant effect after 10–16 hours. On the other hand, when subjects were tested sooner after administration impairment was more striking. In the same study, subjects who ingested temazepam in morning hours experienced significant impairment of visuomotor coordination up to approximately 6.5 hours postadministration. Similar studies also report impairment of visuomotor coordination 2 hours postingestion of 30 mg of temazepam.[14,57] Although temazepam is considered safe by some authors,[51] its detrimental effects on visuomotor coordination may extend up to 12 hours postadministration. Consequently the U.S. Army discourages the use of temazepam as a sleep aid in situations requiring completion of certain complex tasks (e.g., helicopter flight) within 12 hours of administration.[3]

As is the case with other tranquilizer and hypnotic drugs (diazepam, oxazepam, triazolam, and botizolam), there is no evidence that temazepam reentrains physiological and behavioral rhythms, such as those of body core temperature and performance, to new work schedules or LD cycles. Its value, in terms of combatting desynchronosis symptomology, resides in the induction of sleep and the consequent reduction of fatigue in the subsequent day.

Another benzodiazepine, triazolam, has been shown to entrain activity rhythms of the hamster,[36,85] a photoperiodic animal that hibernates and shows gonadal regression during the short days of winter. Most of the reported effects of triazolam on hamster activity rhythms, particularly those involving changes in the length of the period of the rhythm, were induced in constant lighting conditions (either darkness or light) or with blind subjects. These experimental results must be interpreted with caution and very carefully generalized for clinical applications.

To date there is no evidence that triazolam actually resynchronizes human circadian rhythms by directly influencing the timing of the CTS. Although, triazolam has been recently recommended for study and use in combatting desynchronosis,[64] the drug has been shown to impair cognitive function 1 hour (0.125-mg dose)[21] and 8 hours after administration (0.5-mg dose).[60] Its role in the improvement of sleep is also not clear; a 0.5-mg dose of triazolam administered in the laboratory improved the duration and continuity of sleep,[59] but during a less controlled eastward transmeridian troop transport flight, it failed to improve the continuity or to increase the duration of sleep of human subjects.[60]

Xanthene drugs are also potentially useful during transmeridian flights because they are readily available (in coffee, tea, and cola drinks) and have been shown to phase-advance and -delay temperature rhythms in animals, depending on the time of administration (advance: at fall of cycle; delay: at rise of cycle). Rats given an intraperitoneal injection of 1,3-dimethylxanthene (aminophylline; 7.5 mg/100 g) showed a phase advance of the body core temperature rhythm of 5–7 hours and, in other cases, a phase delay up to approximately 12 hours.[23] In addition, these animals exhibited a dramatic reduction of body temperature after receiving injections of trimethylxanthene. This effect is pharmacologically induced; it does not physiologically influence CTS phase status.

The use of caffeine to delay sleep onset is a common practice. However, in order to mimic the effects obtained by Ehret and co-workers[23] in humans, subjects must receive comparably large doses of caffeine. A cup of coffee contains approximately 100 mg of trimethylxanthene (i.e., caffeine), tea contains a bit less, and a cola has approximately 50 mg. Ehret's dose corresponds to approximately 5¼ g for a 70-kg person. Consequently, a cup of coffee before bedtime may delay sleep onset but may not affect the phase of the CTS and dependent rhythms unless the right amount of caffeine is ingested. Over-the-counter, high-caffeine drugs designed to fight sleepiness may be useful when sleep onset must be delayed in order to adopt a new sleep/wake schedule.

Other Alternatives. **Nomifensine,** an antidepressant drug, has been shown to increase the rate of reentrainment of the body core temperature rhythm of rats with bilateral SCN lesions.[32] Thus in the absence of the SCN, and therefore of the LD cycle timing system, nomifensine may influence the oscillator system associated with the timing of the body core temperature rhythm. In the cases of jet lag and shift lag, the possibility of rapidly readjusting the temperature rhythm implies reestablishment of normal sleep, less fatigue during resynchronization, and improved performance during the first days after time zones are crossed or workshift is changed. Research in the use of nomifensine to readjust body temperature rhythms is inconclusive but deserves further attention.

Quiadon (3-alkylpyrazolyl piperazine), a tranquilizer that depletes serotonin availability, has also been tested as a possible chronobiotic.[74,75] Subjects exposed to a simulated 8-hour phase shift of the LD cycle were given approximately a 10-mg dose of Quiadon or placebo just before the new sleep period. During the sleep period, these subjects exhibited fewer awakenings than control subjects given a placebo. Although the two groups did not differ upon awakening in terms of subjective rating of restfulness, subjects given placebos were more tired on retiring. Quiadon may be a potentially useful sleep-inducing drug, and its use may reduce fatigue in the context of jet lag or shift lag. Little is known of the effects of this drug on cognitive performance and timing of body core temperature rhythms. Consequently, its possibility as an effective chronobiotic is still unclear.

Research on tranquilizing drugs of similar biochemical structure may provide viable alternatives to the use of benzodiazepines.

Future Alternatives. An alternative to the use of benzodiazepines, antidepressants, or tranquilizers entails the hormone **melatonin.** In humans, as well as in other species (rodents, lizards, and nonhuman primates), melatonin is synthesized in the pineal gland in the dark phase of the light/dark cycle (during sleep in humans). Exogenously administered melatonin has been shown to induce a slowing of the EEG, sleep, vivid dreams, and a reduction of tremors in patients with Parkinson's disease.[7,8,20]

In 1983 Redman and co-workers[62] showed that exogenously administered melatonin influenced entrainment of activity rhythms in albino rats. Preliminary data in studies of single human subjects suggest that melatonin may increase the rate of readjustment of the CTS after a rapid change in the phase of the LD cycle without undesirable physiological effects.[73] Short and Armstrong[73] reported that 5 mg of melatonin administered 20 minutes before bedtime and upon awakening in the middle of the sleep period induced sleep and rapid reentrainment of body core temperature rhythms after transmeridian flights. In the day after the flight, subjects reported feeling rested and capable of performing academic functions. Petrie and co-workers[61] recently showed that administration of 5 mg of melatonin once a day 3 days before an eastward transmeridian flight, both during the flight and for 3 days after arrival, significantly reduced feelings of fatigue and inertia and facilitated reestablishment of normal sleep patterns.

Short[72] reported evidence in a single-subject experiment that melatonin facilitates rapid adjustment of the acrophase of body core temperature to the dark phase of the LD cycle, thus promoting the daytime synchronization of the sleep period. However, further research efforts must confirm this hypothesis because, unlike jet lag, nightworker shift lag involves the additional problem of sleeping during daytime hours and thus requires a permanent reversal of temperature and activity/rest rhythms with relation to the environmental rhythm of day and night. At present, the use of this hormone in the facilitation of rapid adaptation to shifts from day- to nightwork schedules requires more extensive investigation. Although melatonin currently remains in experimental status in the United States, its future use to combat desynchronosis is probable, particularly because there are indications that, unlike benzodiazepines, melatonin appears to directly affect the status of the CTS.

SUMMARY

Jet lag and shift lag affect many employees in our fast-paced working world. Understanding circadian rhythm desynchronosis is important for successful implementation of coping strategies. The complex interaction between endogenous physiological rhythms and exogenous entraining rhythms (e.g., the light/dark cycle and the timing of eating and fasting) must be acknowledged in evaluating the prevention of jet lag, shift lag, or a combination of the two. Jet lag and shift lag have similar physiological consequences; both result in fatigue, loss of sleep, gastrointestinal disorders, and reduced performance. Jet lag is short lived (it generally lasts fewer than 3 days but can last as long as 18 days); it varies with the number of time zones crossed, individual differences in rhythm chronotype, and the number of days of layover before the return flight. In contrast, shift lag constitutes a more complex problem, particularly in cases where the LD cycle must remain in the opposite phase position from the duty/rest schedule. The severity and persistence of this syndrome also depends on the direction of the shift change (e.g., dayshift to nightshift or daylight to evening work), individual differences, and the number of days scheduled on a given shift (e.g., fixed shifts, slow rotations, fast rotations). The most severe desynchronosis may be experienced by airline personnel involved in transmeridian flights. The jet-lag syndrome can be exacerbated by shift lag depending on the schedule of return flights and on the contiguity of subsequent assignments.

Eastward travelers, in particular, can expect difficulty in readjusting to the destination schedule because the light/dark cycle and life events occur earlier relative to preflight clock times. The general coping strategy is to quickly adopt the destination schedules for sleep and meal times, as well as for social activities. Hypnotic drugs such as benzodiazepines (e.g., temazepam) may serve to induce sleep, but they do not resynchronize the CTS. Use of sleep aids must be carefully monitored because side effects may impact complex cognitive or visuomotor task performance upon awakening and also because repeated use carries some risk of addiction. A less risky sleep induction aid is the timely consumption of carbohydrate-rich meals.

On the other hand, the westward traveler has only to phase-delay sleep and meal times to the destination schedule. This is relatively easier than a phase advance and can be facilitated with readily available substances such as tea, coffee, or over-the-counter caffeine tablets. Meals rich in proteins rather than carbohydrates may also prolong wakefulness until the desired sleep time.

Shift lag poses a more difficult problem than jet lag, although the general strategy for coping with it is similar. The first step is to ensure that during the transition to a new workshift, a new sleep schedule is quickly established. In this case, the direction of the shift (e.g., phase delay: days to evenings, or phase advance: days to nights) determines the degree of difficulty associated with the implementation of the new sleep/wake schedule. In any case, pharmacological aids should be used with particular caution because adjustment to long-term shift rotation may lead workers to abuse benzodiazepines inadvertently. The best strategy for shift lag may be the application of circadian principles by employers to the development of shift schedules. Using rhythm chronotype screening, implementing phase delay rotations, and using fixed, fast, and slow rotating shifts as determined by personnel characteristics and mission significantly ameliorate the impact of shift lag on the individual and ultimately on the organization.

Current research efforts to elucidate the mechanism of action of the circadian timing system and to identify various contributing biological clocks promise future solutions for coping with desynchronosis. For example, research on melatonin to facilitate resynchronization of the body temperature rhythm suggests that interventions in the biosynthesis of this hormone or exogenous administrations of it may be useful in combatting symptoms related to desynchronosis.

Until these and other questions are answered, however, desynchronosis can be best managed by educating workers, employers, labor and management representatives, and occupational specialists about the issues associated with the symptomology and mechanism of generation of the jet-lag and shift-lag syndromes.

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REFERENCES

1. Aanonsen A: Shift Work and Health. Oslo, Universitetsforlaget, 1964.
2. Akerstedt T: Adjustment of physiological circadian rhythms and the sleep-wake cycle to shiftwork. In Folkard S, Monk TH (eds): Hours of Work. New York, John Wiley, 1985, pp 185–197.
3. Alfonso C: Halcion (triazolam). Soc U S Army Flight Surgeons Newsletter 3(4):2, 1989.
4. Alluisi EA, Morgan BB: Temporal factors in human performance and productivity. In Alluisi EA, Fleishman EA (eds): Human Performance and Productivity. Vol 3. Stress and Performance Effectiveness. Hillsdale, NJ: Lawrence Erlbaum, 1982, pp 165–247.
5. Andlauer P, Reinberg A: Amplitude of the oral temperature circadian rhythm and tolerance of shiftwork. Chronobiologia 6:67–73, 1979.
6. Angersbach D, Knauth P, Loskant H: A retrospective cohort study comparing complaints and diseases in day and shift workers. Int Arch Occup Environ Health 45:127-140, 1980.
7. Anton-Tay F: On the effect of melatonin upon the human brain: Its possible therapeutic implications. Life Sci 10:841–850, 1971.
8. Anton-Tay F: Melatonin: Effects on brain function. Adv Biochem Psychopharmacol 11:315–424, 1974.
9. Aschoff J: Internal dissociation and desynchronization of circadian systems. Twenty-first International Congress of Aviation and Space Medicine, preprint 255, 1973.
10. Aschoff J: Problems of re-entrainment of circadian rhythms: Asymmetry effect, dissociation and partition. In Assenmacher J, Farner DS (eds): Environmental Endocrinology. New York, Springer Verlag, 1978, pp 185–195.
11. Aschoff J: Circadian rhythms within and outside their ranges of entrainment. In Assenmacher J, Farner DS (eds): Environmental Endocrinology. New York, Springer Verlag, 1978, pp 172–181.
12. Beljan JR, Rosenblatt LS, Hetherington NW, et al: Human performance in the aviation environment. Final report (five parts). NASA Contract NAS2-6657, 1972.
13. Breimer DD: Pharmacokinetics and metabolism of various benzodiazepines used as hypnotics. Br J Clin Pharmacol 8:7–13, 1979.
14. Clark CH, Nicholson AN: Immediate and residual effects in man of the metabolites of diazepam. Br J Clin Pharmacol 6:325–332, 1978.
15. Coleman RM: Wide Awake at 3:00 A.M.: By Choice or by Chance? New York, W.H. Freeman, 1986.
16. Colquhoun WP: Phase shift in temperature rhythm after transmeridian flight, as related to preflight phase angle. Int Arch Occup Environ Health 42:149–157, 1979.
17. Colquhoun WP, Blake MJF, Edwards RS: Experimental studies of shift work. I. A comparison of "rotating" and "stabilizing" 4-hour systems. Ergonomics 11:437–453, 1968a.
18. Colquhoun WP, Blake MJF, Edwards RS: Experimental studies of shift work. III. Stabilized 12-hour shift system. Ergonomics 12:865–882, 1968b.
19. Comperatore CA, Stephan FK: Entrainment of duodenal activity periodic feeding. Biol Rhythms 2(3):227–242, 1987.
20. Cramer H: Melatonin and sleep. In Popoviciu L, Asgian G (eds): Sleep. Basel, Karger, 1980, pp 204–210.

21. Duncan RL, Simon LM, O'Donnell VM, et al: The effect of triazolam on cognitive performance. Abstracts of the 1989 American Psychological Association Annual Convention, New Orleans, 11-15 August 1989.
22. Ehret CF, Groh KR, Meinert JC: Consideration of diet in alleviating jet lag. In Scheving LE, Halberg F (eds): Principles and Applications to Shift in Schedules. Rockville, MD, Sijthoff and Noordhoff, 1980, pp 393–402.
23. Ehret CF, Potter VR, Dobia KW: Chronobiological action of theophylline and of pentobarbital as circadian zeitgebers in the rat. Science 188:1212–1214, 1975.
24. Folkard S: Shiftwork and its effects on performance. In Scheving LE, Halberg F (eds): Chronobiology: Principles and Applications to Shifts in Schedules. Rockville, MD, Sijthoff and Noordhoff, 1980, pp 293-306.
25. Folkard S: Shiftwork and performance. In Johnson LC, Tepas DI, Colquhoun WP, Colligan MJ (eds): Biological Rhythms, Sleep and Shift Work. New York, Spectrum, 1981, pp 283-305.
26. Folkard S, Knauth P, Monk TH, Rutenfranz J: The effect of memory load on the circadian variation in performance efficiency under a rapidly rotating shift system. Ergonomics 19:479–488, 1976.
27. Folkard S, Monk TH: Shiftwork and performance. Hum Factors 21:483–492, 1979.
28. Folkard S, Monk TH: Individual differences in the circadian response to a weekly rotating shift system. In Reinberg A, Vieux N, Andlauer P (eds): Night and Shiftwork: Biological and Social Aspects. Oxford, Pergamon, 1981, pp 367-374.
29. Goetz F, Bishop J, Halberg F, et al: Timing of single daily meal influences relations among human circadian rhythms and urinary cyclic AMP and hemic glucagon, insulin and iron. Experentia 15:1081-1084, 1976.
30. Graeber RC: Alterations in performance following rapid transmeridian flight. In Brown FM, Graeber RC (eds): Rhythmic Aspects of Behavior. London, Lawrence Erlbaum, 1982, pp 173–212.
31. Graeber RC: Aircrew fatigue and circadian rhythmicity. In Weiner EL, Nagel DC (eds): Human Factors in Aviation. New York, Academic Press, 1988, pp 305-344.
32. Halberg F, Lubanovic WA, Brockway B, et al: Nomifensine chronopharmacology, schedule-shifts and circadian temperature rhythms in di-suprachiasmatically lesioned rats: Modeling emotional chronopathology and chronotherapy. Chronobiologia 6:405–424, 1979.
33. Hauty GT, Adams T: Phase shifts of the human circadian system and performance deficit during the periods of transition. III. North-South flight. Aerospace Med 73:1257-1262, 1966.
34. Hildebrandt G, Stratmann I: Circadian system response to night work in relation to the individual circadian phase position. Int Arch Occup Environ Health 43:73-83, 1979.
35. Horne JA, Ostberg O: Individual differences in human circadian rhythms. Biol Psychol 5:179–190, 1977.
36. Joy JE, Losee-Olson S, Turek FW: Single injections of triazolam, a short-acting benzodiazepine, lengthen the period of the circadian activity rhythm in golden hamsters. Experientia 45:152–154, 1989.
37. Klein KE, Bruner H, Holtmann H, et al: Circadian rhythm of pilots' efficiency and effects of multiple time zone travel. Aerospace Med 41:125-132, 1970.
38. Klein KE, Wegmann HM: The resynchronization of human circadian rhythms after transmeridian flights as a result of flight direction and mode of activity. In Scheving LE, Halberg F, Pauly JE (eds): Chronobiology. Toyko, Igaku, 1974, pp 564–570.
39. Klein KE, Wegmann HM: Circadian rhythms in air operations. In Nicholson AN (ed): Sleep, Wakefulness, and Circadian Rhythms. Neuilly sur Seine, France, NATO Advisory Group for Aerospace Research and Development 10.1-10.25, 1979.
40. Klein KE, Wegmann HM: Significance of circadian rhythms in aerospace operations. AGARD dograph no. 247, Advisory Group for Aerospace Research and Development, NATO. London, Technical Editing and Reproduction, 1980.
41. Klein KE, Wegmann HM, Athenassenas G, et al: Air operations and circadian performance rhythms. Aviat Space Environ Med 47:221-230, 1976.
42. Klein KE, Wegmann HM, Hunt BI: Desynchronization of body temperature and performance circadian rhythm as a result of outgoing and homecoming transmeridian flights. Aerospace Med 43:119-132, 1972.
43. Knauth P, Emde E, Rutenfranz J, et al: Reentrainment of body temperature in field studies of shift work. Int Arch Occup Environ Health 49:137-149, 1981.
44. Knauth P, Rutenfranz J: Duration of sleep related to the type of shift work. In Reinberg A, Vieux N, Andlauer P (eds): Night and Shift Work: Biological and Social Aspects. Oxford, Pergamon, 1981.

45. Kogi K: Social aspects of shift work in Japan. Int Labour Rev 104:415–433, 1971.
46. Kogi K: Research motives and methods in field approaches to shift work. In Johnson LC, Tepas DI, Colquhoun WP, Colligan MJ (eds): Biological Rhythms, Sleep and Shift Work. New York, Spectrum, 1981.
47. Kogi K: Introduction to the problems of shiftwork. In Folkard S, Monk TH (eds): Hours of Work. New York, John Wiley, 1985, pp 165–184.
48. Kogi K, Ohta T: Incidence of near accidental drowsing in locomotive driving during a period of rotation. J Hum Ergol (Tokyo) 4:65–76, 1975.
49. Lewy AJ, Wehr TA, Goodwin FK, et al: Light suppresses melatonin secretions in humans. Science 210:1267–1269, 1980.
50. Matejecek M, Neff G, Abt K, et al: Pharmaco-EEG and psychometric study of the effect of single doses of temazepam and nitrazepam. Neuropsychobiology 9:53–65, 1983.
51. McGhee JE: An experimental trial to test the efficacy for temazepam to induce sleep and improve subsequent performance during partial sleep deprivation and circadian rhythm desynchronosis. Defense Technical Information Center no. AD-A160795. Presented to the Faculty of The University of Texas Health Science Center at Houston, TX, 1985.
52. Menzel W: Zur Physiologie und Pathologie des Nacht und Schichtarbeiters. Arbeitsphysiologie 14:304, 1950.
53. Menzel W: Menschliche Tag-Nacht-Rhythmik und Schichtarbeit. Basle, Benno Schabe, 1962.
54. Monk TH: Coping with the stress of jet-lag. Work Stress 1:163–166, 1987.
55. Moore-Ede MC, Sulzman FM, Fuller CA: The Clocks that Time Us: Physiology of the Circadian Timing System. London, Harvard University Press, 1982.
56. Nakano Y, Miura T, Hara I, et al: The effect of shift work on cellular immune function. Proceedings of the 6th International Symposium on Night and Shift Work. J Hum Ergol (Tokyo) 11(suppl), 1982.
57. Nicholson AN: Performance studies with diazepam and its hydroxylated metabolites. Br J Clin Pharmacol 8:39–42, 1979.
58. Nicholson AN, Stone BM: Hypnotics and shift work. In Johnson LC, Tepas DI, Colquhoun WP, Colligan MJ (ed): Biological Rhythms, Sleep and Shift Work. New York, Spectrum, 1981.
59. O'Donnell VM, Balkin TJ, Andrade JR, et al: Effects of triazolam on performance and sleep in a model of transient insomnia. Hum Perform 1:145–160, 1988.
60. Penetar DM, Belenky G, Garrigan JJ, et al: Triazolam impairs learning and fails to improve sleep in a long-range aerial deployment. Aviat Space Environ Med 60:594–598, 1989.
61. Petrie K, Conaglen JV, Thompson L, Chamberlain K: Effects of melatonin on jet lag after long haul flights. Br Med J 298:705–707, 1989.
62. Redman J, Armstrong S, Ng KT: Free-running activity rhythms in the rat: Entrainment by melatonin. Science 219:1089–1091, 1983.
63. Reinberg A, Andlauer P, Guillet P, et al: Oral temperature, circadian rhythm amplitude, aging, and tolerance for shiftwork. Ergonomics 23:55–64, 1980.
64. Reinberg A, Smolensky M, Labrecque G: The hunting of a wonder pill for resetting all biological clocks. Ann Rev Chronopharmacol 4:171-208, 1988.
65. Reinberg A, Vieux N, Ghata J, et al: Amplitude of the oral temperature circadian rhythm in relation to the ability to phase shift circadian rhythms of shift workers. Chronobiology 6(suppl 1):57–63, 1979.
66. Rutenfranz J, Colquhoun WP, Knauth P, Ghata JN: Biomedical and psychological aspects of shift work. Scand J Work Environ Health 3:165–182, 1977.
67. Rutenfranz J, Knauth P, Colquhoun WP: Hours of work and shiftwork. Ergonomics 19:331-340, 1976.
68. Rutenfranz J, Knauth P, Kupper R, et al: Pilot project on the physiological and psychological consequences of shiftwork in some branches of the services sector. In The Effects of Shiftwork on Health, Social and Family Life. Dublin, European Foundation for the Improvement of Living and Working Conditions, 1981.
69. Saito H: Rodo jikan, kyukei, kotaisei. Tokyo, Institute for Science of Labour, 1954.
70. Scheving LE, Tsai TH, Scheving LA: Chronobiology of the intestinal tract of the mouse. Am J Anat 168:433–465, 1983.
71. Shift Work Committee, Japan Association of Industrial Health: Opinion on night work and shift work. J Sci Labour Part II:1-36, 1979.
72. Short RV: Method for minimizing disturbances in circadian rhythms of bodily performance and function. U.S. Patent No. 4,600,723 (Jul 15, 1986). Washington, DC, U.S. Patent Office.

73. Short RV, Armstrong S: Method for minimizing disturbances in circadian rhythms of bodily performance and function. U.S. Patient No. 4,665,086 (May 12, 1987). Washington, DC, U.S. Patent Office.
74. Simpson HW: Chronobiotics: Selected agents of potential value in jet lag and other dyschronisms. In Scheving LE, Halberg F: Chronobiology Principles and Applications to Shifts in Schedules. Rockville, MD, Sijthoff and Noordhoff, 1980.
75. Simpson HW, Bellamy N, Halberg F: Double blind trial of a possible chronobiotic (quiadon): Field studies in N.W. Greenland. Int J Chronobiol 1:287-311, 1973.
76. Stepanova SI: Effect of transmeridianal flight on the human body. Kosm Biol Aviakosm Med 8:3-12, 1974.
77. Stepanova SI: Biorhythmic selection of cosmonauts. Kosm Biol Aviakosm Med 9:40-46, 1975.
78. Stepanova SI: Problems of Space Biology: Current Problems in Space Biorhythmology. Moskow, Izdatel'stvo Nauka, 1977. (In Russian)
79. Taylor PJ, Pocock SJ: Mortality of shift and day workers 1956-1968. Br J Ind Med 29:201-207, 1972.
80. Taylor PJ, Pocock CJ, Sergean R: Absenteeism of shift and day workers. Br J Ind Med 29:208-213, 1972.
81. Teleky L: Problems of night work: Influences on health and efficiency. Ind Med Surg 12:758, 1943.
82. Tepas DI: Shiftwork sleep strategies. J Hum Ergol (Tokyo) 11(suppl):325-336, 1982.
83. Tepas DI, Monk TH: Work schedules. In Salvendy G (ed): Handbook of Human Factors. New York, John Wiley, 1987.
84. Van Loon JH: Diurnal body temperature curves in shift workers. Ergonomics 6:267-273, 1963.
85. Van Reeth O, Turek FW: Administering triazolam on a circadian basis entrains the activity rhythm of hamsters. Am J Physiol 25:256-263, 1989.
86. Wever RA: The Circadian System of Man. Results of Experiments under Temporal Isolation. New York, Springer Verlag, 1979.
87. Wever RA: Phase shifts of human circadian rhythms due to shifts of artificial zeitgebers. Chronobiology 7:303-327, 1980.
88. Winget CM, DeRoshia CW, Markley CL, Holley DC: A review of human physiological and performance changes associated with desynchronosis of biological rhythms. Aviat Space Environ Med 55(12):1085-1093, 1984.
89. Wojtczak-Jaroszowa J: Circadian rhythm of biological functions and night work. In Wojtczak-Jaroszowa J (ed): Physiological and Psychological Aspects of Night and Shift Work. Cincinnati, National Institute for Occupational Safety and Health, 1977, pp 3-12.